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=> s bronchial constriction
L1 519 BRONCHIAL CONSTRICTION

=> s l1 and treatment
L2 74 L1 AND TREATMENT

=> s l2 and "light chain binding peptide"
L3 0 L2 AND "LIGHT CHAIN BINDING PEPTIDE"

=> s l2 and THP
L4 0 L2 AND THP

=> s l2 and Tamm Horsfall glycoprotein
L5 0 L2 AND TAMM HORSFALL GLYCOPROTEIN

=> s LCBP or Tamm horsfall glycoprotein
L6 1904 LCBP OR TAMM HORSFALL GLYCOPROTEIN

=> s l6 and
MISSING TERM AFTER L6 AND
Operators must be followed by a search term, L-number, or query name.

=> s l6 adn "AHWSGHCCL"
MISSING OPERATOR L6 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l6 and "AHWSGHCCL"
L7 5 L6 AND "AHWSGHCCL"

=> dup remove l7
PROCESSING COMPLETED FOR L7
L8 1 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 cbib abs

L8 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
97197581 Document Number: 97197581. PubMed ID: 9045877. Localization of a
single binding site for immunoglobulin light chains on human **Tamm**
-Horsfall glycoprotein. Huang Z Q; Sanders P W.
(Department of Veterans Affairs Medical Center, Birmingham, Alabama 35233,
USA.) JOURNAL OF CLINICAL INVESTIGATION, (1997 Feb 15) 99 (4) 732-6.
Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States.

Language: English.

AB Cast nephropathy is a severe complication of multiple myeloma. Binding of filtered monoclonal light chains (LC) with **Tamm-Horsfall glycoprotein** (THP) triggers heterotypic aggregation of these two proteins to form casts in the distal nephron of the kidney. To localize the LC binding site on THP, human THP was deglycosylated and underwent limited trypsin digestion in the presence or absence of a nephrotoxic LC known to bind THP. A 29.6-kD band was protected from trypsin digestion by the addition of LC. NH₂-terminal amino acid sequence and amino acid analyses revealed this band was located between the 6th and 287th amino acid residues of THP. Six peptides located within this 29.6-kD fragment were synthesized and used as potential inhibitors of binding or aggregation of five different nephrotoxic LCs with THP. Peptide **AHWSGHCCCL** (from amino acid 225 to 233) completely inhibited binding and aggregation of these proteins. Optimal inhibition required a cysteine residue in this peptide. Truncation experiments demonstrated the entire sequence was necessary for ideal inhibition and the histidine residue explained the effects of pH on binding. These studies provided a basis for further study of LC-THP interaction and a potential approach toward the prevention of cast nephropathy.

=> s excipient

L9 22570 EXCIPIENT

=> s l9 and tween 20

L10 95 L9 AND TWEEN 20

=> s l10 and PBS

L11 1 L10 AND PBS

=> d l11 cbib abs

L11 ANSWER 1 OF 1 MEDLINE on STN

2001297619 Document Number: 21272629. PubMed ID: 11376976. Development of a novel dosage form for intramuscular injection of titrated extract of *Centella asiatica* in a mixed micellar system. Kim C; Hwang Y Y; Chang J Y; Choi H G; Lim S J; Lee M K. (College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Ku, 151-742, Seoul, South Korea.. cckim@plaza.snu.ac.kr) . INTERNATIONAL JOURNAL OF PHARMACEUTICS, (2001 Jun 4) 220 (1-2) 141-7. Journal code: 7804127. ISSN: 0378-5173. Pub. country: Netherlands. Language: English.

AB Titrated extract of *Centella asiatica* (TECA), a drug used in treating systemic scleroderma, is poorly water-soluble. A conventional dosage form for the intramuscular injection of TECA, propylene glycol (PG)-based TECA solution, causes severe pain after intramuscular injection. To improve the solubility of TECA and reduce pain after injection, mixed micellar systems composed of 10% surfactant mixture (**Tween 20** and **Tween 85**) and 90% phosphate-buffered saline, pH 7.0 (**PBS**) were prepared. As the ratio of **Tween 20** to **Tween 85** increased from 0:10 to 10:0, the solubility of TECA in the mixed micellar systems increased from 7- to 26-fold compared to that in **PBS** (pH 7.0). The droplet size of micelles gradually decreased with the increasing ratio of **Tween 20** to **Tween 85** from 0:10 to 4:6, followed by an abrupt decrease in size above the ratio of 6:4. Furthermore, the micellar systems prepared with **Tween 20** and **Tween 85** at the ratio of 6:4, 8:2 or 10:0 could solubilize TECA more than 10 mg/ml and the resultant droplet sizes were less than 2 microm. No significant changes were observed in the droplet sizes and asiaticoside contents in these micellar formulations during storage, indicating these systems are stable for at least 60 days. Their osmotic pressures were remarkably lower than those of PG-based TECA solution and similar to that of saline solution, irrespective of dilution ratios. Most importantly, they markedly reduced the number of writhes compared with PG-based TECA solution after injection to mice. All of these results suggest that these

three TECA micellar formulations prepared with **Tween 20** and Tween 85 improved the solubility of TECA and reduced pain following injection, possibly due to the decrease in osmotic pressure. Thus, these micellar formulations composed of optimum ratios of **Tween 20** and Tween 85 may have a potential as dosage forms for the intramuscular injection of a poorly water-soluble TECA.

=> s free light chain immunoglobulin

L12 24 FREE LIGHT CHAIN IMMUNOGLOBULIN

=> s l12 and disease

L13 11 L12 AND DISEASE

=> dup remove l13

PROCESSING COMPLETED FOR L13

L14 8 DUP REMOVE L13 (3 DUPLICATES REMOVED)

=> d l14 1-8 cbib abs

L14 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN

2002:493237 Document No. 137:107976 Immunoglobulin-free light chains elicit immediate hypersensitivity-like responses. Redegeld, Frank A.; van der Heijden, Maurice W.; Kool, Mirjam; Heijdra, Bianca M.; Garssen, Johan; Kraneveld, Aletta D.; van Loveren, Henk; Roholl, Paul; Saito, Takashi; Verbeek, J. Sjef; Claassens, Jill; Koster, Andries S.; Nijkamp, Frans P. (Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacology and Pathophysiology, Utrecht University, Utrecht, Neth.). Nature Medicine (New York, NY, United States), 8(7), 694-701 (English) 2002. CODEN: NAMEFI. ISSN: 1078-8956. Publisher: Nature Publishing Group.

AB Ig-free light chains IgLC are present in serum and their prodn. is augmented under pathol. conditions such as multiple sclerosis, rheumatoid arthritis and neurol. disorders. Until now, no pathophysiol. function has been ascribed to circulating Ig light chains. Here the authors show that IgLCs can confer mast cell-dependent hypersensitivity in mice. Antigenic stimulation results in plasma extravasation, cutaneous swelling and mast-cell degranulation. The authors show that IgLCs have a crucial role in development of contact sensitivity, which could be completely prevented by a novel IgLC antagonist. Although IgE and IgG1 are central to the induction of immediate hypersensitivity reactions, the authors' results show that IgLCs have similar activity. IgLCs may therefore be a novel factor in the humoral immune response to antigen exposure. Our findings open new avenues in investigating the pathogenesis of autoimmune diseases and their treatments.

L14 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2001:314918 Document No.: PREV200100314918. Polyclonal free light chains (PFLC) of immunoglobulin in urine of patients with SLE. Ramos, S. [Reprint author]; Coromina, G. [Reprint author]; Pacheco, G. [Reprint author]; Mannucci, P. [Reprint author]; Ubieta, C. [Reprint author]; Di Lonardo, A. M. [Reprint author]. Unidad Inmunologia, Hospital Dr. C. G. Durand, Buenos Aires, Argentina. *Lupus*, (2001) Vol. 10, No. Supplement 1, pp. S117. print. Meeting Info.: Sixth International Lupus Conference. Barcelona, Spain. March 24-28, 2001. ISSN: 0961-2033. Language: English.

L14 ANSWER 3 OF 8 MEDLINE on STN

97342093 Document Number: 97342093. PubMed ID: 9245156. [Free light-chain immunoglobulins in the biological fluids of patients with multiple sclerosis]. Svobodnye legkie tsepi immunoglobulinov v biologicheskikh zhidkostiakh bol'nykh rasseiannym sklerozom. Totolian N A; Griazeva I V; Klimovich V B; Totolian A A. *ZHURNAL NEVROPATOLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA*, (1997) 97 (5) 34-8. Journal code: 8710066. ISSN: 0044-4588. Pub. country: RUSSIA:

Russian Federation. Language: Russian.

- AB 15 patients with clinically significant multiple sclerosis (MS) were examined in terms of content of free light chains of immunoglobulins of kappa- and lambda-types in blood serum, cerebrospinal liquor, lacrimal fluid, saliva, urine, indices were compared with corresponding data of 12 patients with other neurological **diseases** and of 10 healthy individuals (control group). Significantly increased content of kappa-chains in cerebrospinal, lacrimal fluids and urine was revealed in patients with MS as compared with other two groups and in saliva of patients as compared with controls. The frequency of alterations was high in all biological fluids of the patients with MS. Elevated content of kappa-chains was most often observed in cerebrospinal fluid of the patients (13 individuals). The changes observed reflected systemic activation of humoral immune response in MS. Examination of cerebrospinal fluid was most informative for differential diagnosis.

L14 ANSWER 4 OF 8 MEDLINE on STN
96367556 Document Number: 96367556. PubMed ID: 8771670. [The clinical significance of **free light-chain immunoglobulins**]. Klinicheskoe znachenie svobodnykh legkikh tsepei immunoglobulinov. Kamaeva O I; Reznikov Iu P. TERAPEVTICHESKII ARKHIV, (1996) 68 (2) 78-81. Ref: 29. Journal code: 2984818R. ISSN: 0040-3660. Pub. country: RUSSIA: Russian Federation. Language: Russian.

L14 ANSWER 5 OF 8 MEDLINE on STN
96222830 Document Number: 96222830. PubMed ID: 8644033. [Monoclonal **free light-chain immunoglobulins**: their clinical interpretation]. Monoklonal'nye svobodnye legkie tsepi immunoglobulinov: klinicheskaya interpretatsiya. Reznikov Iu P; Kamaeva O I; Pimenova N S. TERAPEVTICHESKII ARKHIV, (1996) 68 (1) 52-4. Journal code: 2984818R. ISSN: 0040-3660. Pub. country: RUSSIA: Russian Federation. Language: Russian.

- AB 23 cases of free light chains (FLC) occurrence in the blood and/or urine in the absence of monoclonal gammopathy are reported. Of them 15 cases were attributed to renal **diseases** associated with deranged catabolism of low-molecular proteins including FLC. In the rest cases FLC hyperproduction in autoimmune **diseases** was suspected to cause FLC appearance. No correlation was found between the amounts of FLC, creatinine, beta 2-microglobulin, light chains, kappa/lambda proportions.

L14 ANSWER 6 OF 8 MEDLINE on STN
95028334 Document Number: 95028334. PubMed ID: 7941891. [The content of **free light-chain immunoglobulins** in the cerebrospinal fluid and the importance of its determination for the differential diagnosis of multiple sclerosis]. Soderzhanie svobodnykh legkikh tsepei immunoglobulinov v likvore i znachenie ego opredeleniya dlia differentsial'noi diagnostiki rasseiannogo skleroza. Totolian N A; Griazeva I V; Klimovich V B; Skoromets A A. ZHURNAL NEVROLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA, (1994) 94 (2) 49-53. Journal code: 8710066. ISSN: 0044-4588. Pub. country: RUSSIA: Russian Federation. Language: Russian.

- AB The serum and liquor of 70 patients with multiple sclerosis (MS), 54 patients with other neurological **diseases** and 20 controls were examined for free light chains (FLC) of immunoglobulins type chi and lambda. The findings were compared to blood-brain barrier competence, liquor pleocytosis, IgG intrathecal synthesis 86% MS patients exhibited high levels of liquor chi-type FLC which appeared early in the **disease** course irrespectively of MS phase and pattern. Simultaneous high content of lambda-type FLC was reported in 52% of the cases. Patients in need of differential diagnosis were characterized by normal or reduced (in spinocerebellar ataxia) concentrations of FLC except for the conditions with impaired blood-brain barrier.

L14 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 1
94192048 Document Number: 94192048. PubMed ID: 8143195. Urine levels of

soluble interleukin 2 receptor and **free light chain immunoglobulins** in lupus nephritis. Ling S H. (Renal Research Institute, Sun Yat-Sen University of Medical Sciences, Guangzhou.) CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], (1993 Dec) 73 (12) 756-8, 774. Journal code: 7511141. ISSN: 0376-2491. Pub. country: China. Language: Chinese.

AB To find out the relationship between soluble interleukin 2 receptor (sIL-2R) or **free light chain immunoglobulins** (FLCI) and the activity of lupus nephritis (LN), we determined sIL-2R by ELISA and FLCI by immunodiffusion in the urine of 30 patients with LN and 20 normal persons. We also studied the correlation of sIL-2R levels with clinical and serologic findings over 3 months in the patients. sIL-2R was significantly higher in the active LN patients (160 +/- 108U/ml) than in the normal controls (85 +/- 19U/ml, P < 0.01) and in the inactive LN patients (92 +/- 23 U/ml, P < 0.05), but their serum complements did not change significantly. The positive rate of urine FLCI was higher in the active LN patients than in the inactive LN patients (77% to 15%, P < 0.01) and the normal controls (negative). These results suggest that the urine sIL-2R and FLCI are sensitive markers for **disease** activity in LN.

L14 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 2
89359771 Document Number: 89359771. PubMed ID: 2504765. Clinical relapse in systemic lupus erythematosus: correlation with antecedent elevation of urinary **free light-chain immunoglobulin**. Hopper J E; Sequeira W; Martellotto J; Papagiannes E; Perna L; Skosey J L. (Section of Hematology, University of Illinois College of Medicine, Chicago 60680.) JOURNAL OF CLINICAL IMMUNOLOGY, (1989 Jul) 9 (4) 338-50. Journal code: 8102137. ISSN: 0271-9142. Pub. country: United States. Language: English.

AB This paper reports preliminary evidence suggesting that measurements of free light-chain Ig (FLIg) in urine may represent quantitative markers of in vivo polyclonal B-cell activation. Thus, longitudinal levels of urinary FLIg in patients with systemic lupus erythematosus (SLE) may be used to track or monitor the in vivo immunopathologic B-cell activity of SLE and be helpful in predicting a **disease** relapse. Our findings showed that dramatic rises in urinary FLIg occurred during asymptomatic intervals that preceded by 4-8 weeks the first symptomatic signs of acute SLE relapse. These results suggest that a sizable lead time may exist between the occurrence of immunopathologic B-cell stimulation and the resultant symptoms and tissue damage of immune complex-induced acute inflammation. In these studies the measurement of urinary FLIg was accomplished by an indirect method using ng-sensitive radioimmunoassays (RIAs) that measured isotypic IgG, IgA, IgM, total kappa-Ig, and total lambda-Ig. As a control for the assessment of renal tubular function and the excretion of low molecular weight proteins in SLE patients, longitudinal measurements of beta-2-microglobulin (B2M) and lysozyme were made using a novel solid-phase 3H-biotin RIA technique.

=> s "AHWSGHCCL"

L15 5 "AHWSGHCCL"

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L16 1 DUP REMOVE L15 (4 DUPLICATES REMOVED)

=> d l16 cbib abs

L16 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
97197581 Document Number: 97197581. PubMed ID: 9045877. Localization of a single binding site for immunoglobulin light chains on human Tamm-Horsfall glycoprotein. Huang Z Q; Sanders P W. (Department of Veterans Affairs Medical Center, Birmingham, Alabama 35233, USA.) JOURNAL OF CLINICAL INVESTIGATION, (1997 Feb 15) 99 (4) 732-6. Journal code: 7802877. ISSN:

0021-9738. Pub. country: United States. Language: English.
AB Cast nephropathy is a severe complication of multiple myeloma. Binding of filtered monoclonal light chains (LC) with Tamm-Horsfall glycoprotein (THP) triggers heterotypic aggregation of these two proteins to form casts in the distal nephron of the kidney. To localize the LC binding site on THP, human THP was deglycosylated and underwent limited trypsin digestion in the presence or absence of a nephrotoxic LC known to bind THP. A 29.6-kD band was protected from trypsin digestion by the addition of LC. NH2-terminal amino acid sequence and amino acid analyses revealed this band was located between the 6th and 287th amino acid residues of THP. Six peptides located within this 29.6-kD fragment were synthesized and used as potential inhibitors of binding or aggregation of five different nephrotoxic LCs with THP. Peptide **AHWSGHCCL** (from amino acid 225 to 233) completely inhibited binding and aggregation of these proteins. Optimal inhibition required a cystine residue in this peptide. Truncation experiments demonstrated the entire sequence was necessary for ideal inhibition and the histidine residue explained the effects of pH on binding. These studies provided a basis for further study of LC-THP interaction and a potential approach toward the prevention of cast nephropathy.

=> s (redegeld f?/au or draneveld a?/au or nkjkamp f?/au)
L17 238 (REDEGELD F?/AU OR DRANEVELD A?/AU OR NKJKAMP F?/AU)

=> s l17 and human Tamm-horsfall glycoprotein
L18 0 L17 AND HUMAN TAMM-HORSFALL GLYCOPROTEIN

=> s l17 and immunoglobulin light chains
L19 4 L17 AND IMMUNOGLOBULIN LIGHT CHAINS

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L20 4 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d l20 1-4 cbib abs

L20 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
2003:719517 Document No. 139:244723 **Ig light chains** mediate hypersensitivity. Nijkamp, Franciscus Petrus; Redegeld, Franciscus Antonius Maria; Kraneveld, Aletta Desiree; Van De Winkel, Johannes Gerardus Joseph; Vidarsson, Gestur (Fornix Biosciences N.V., Neth.). PCT Int. Appl. WO 2003074563 A2 20030912, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-NL167 20030305. PRIORITY: EP 2002-75874 20020306; US 2002-PV362040 20020306; EP 2002-77352 20020614.

AB **Ig light chains** (Ig-LC) are produced in excess in animals compared to heavy chains. The present invention implicates these Ig-LC in hypersensitivity responses and provides means and methods for manipulating the responses. The invention further provides a common gamma chain independent receptor on mast cells capable of mediating the mentioned effects of Ig-LC. In response to activation of the pathway of which the found receptor is a part, a mast cell is activated and stimulated to degranulate.

L20 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
2003:717226 Document No. 139:229273 **Ig light chains** mediate hypersensitivity responses. Nijkamp, Franciscus

Petrus; Kraneveld, Aletta Desire; Redegeld, Franciscus Antonius Maria (Fornix Biosciences N. V., Neth.). Eur. Pat. Appl. EP 1342779 A1 20030910, 33 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-75874 20020306.

AB **Ig light chains** (Ig-LC) are produced in excess in animals compared to heavy chains. The present invention implicates these Ig-LC in hypersensitivity responses and provides means and methods for manipulating the responses. The invention further provides a receptor on mast cells capable of mediating the mentioned effects of Ig-LC.

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

2002:493237 Document No. 137:107976 Immunoglobulin-free light chains elicit immediate hypersensitivity-like responses. Redegeld, Frank A.; van der Heijden, Maurice W.; Kool, Mirjam; Heijdra, Bianca M.; Garssen, Johan; Kraneveld, Aletta D.; van Loveren, Henk; Roholl, Paul; Saito, Takashi; Verbeek, J. Sjef; Claassens, Jill; Koster, Andries S.; Nijkamp, Frans P. (Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacology and Pathophysiology, Utrecht University, Utrecht, Neth.). Nature Medicine (New York, NY, United States), 8(7), 694-701 (English) 2002. CODEN: NAMEFI. ISSN: 1078-8956. Publisher: Nature Publishing Group.

AB Ig-free light chains IgLC are present in serum and their prodn. is augmented under pathol. conditions such as multiple sclerosis, rheumatoid arthritis and neurol. disorders. Until now, no pathophysiol. function has been ascribed to circulating **Ig light chains**. Here the authors show that IgLCs can confer mast cell-dependent hypersensitivity in mice. Antigenic stimulation results in plasma extravasation, cutaneous swelling and mast-cell degranulation. The authors show that IgLCs have a crucial role in development of contact sensitivity, which could be completely prevented by a novel IgLC antagonist. Although IgE and IgG1 are central to the induction of immediate hypersensitivity reactions, the authors' results show that IgLCs have similar activity. IgLCs may therefore be a novel factor in the humoral immune response to antigen exposure. Our findings open new avenues in investigating the pathogenesis of autoimmune diseases and their treatments.

L20 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

2000:53707 Document No. 132:106970 Compound capable of inhibiting the binding of a protein to mast cells, use of the compound for the preparation of a drug, a pharmaceutical composition, a method of diagnosing a disease, and a method of selection. Redegeld, Franciscus Antonius Maria; Kraneveld, Aletta Desiree; Nijkamp, Franciscus Petrus (Universiteit Utrecht, Neth.). PCT Int. Appl. WO 2000002915 A1 20000120, 27 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-NL430 19990707. PRIORITY: NL 1998-1009601 19980709.

AB The invention relates to a compd. inhibiting the binding of the free light chain of Ig (Ig LC) to mast cells. It has been found that Ig LC is the agent responsible for the sensitization of mast cells. The compds. according to the invention can thus be used for the prepn. of a drug for the treatment of a disease whose symptom is an elevated Ig LC concn. in serum or spinal fluid. The invention also relates to a method of screening a series of compds. on their ability to reduce the sensitization of mast cells.

=> s autoimmune disease adn Ig-LC
L21 0 AUTOIMMUNE DISEASE ADN IG-LC

=> s autoimmune disease and Ig-LC
L22 0 AUTOIMMUNE DISEASE AND IG-LC

=> s "Ig-LC"
L23 29 "IG-LC"

=> s l23 and excipient
L24 0 L23 AND EXCIPIENT

=> dup remove l23
PROCESSING COMPLETED FOR L23
L25 13 DUP REMOVE L23 (16 DUPLICATES REMOVED)

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L25 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
2003:719517 Document No. 139:244723 Ig light chains mediate hypersensitivity. Nijkamp, Franciscus Petrus; Redegeld, Franciscus Antonius Maria; Kraneveld, Aletta Desiree; Van De Winkel, Johannes Gerardus Joseph; Vidarsson, Gestur (Fornix Biosciences N.V., Neth.). PCT Int. Appl. WO 2003074563 A2 20030912, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-NL167 20030305. PRIORITY: EP 2002-75874 20020306; US 2002-PV362040 20020306; EP 2002-77352 20020614.

AB Ig light chains (**Ig-LC**) are produced in excess in animals compared to heavy chains. The present invention implicates these **Ig-LC** in hypersensitivity responses and provides means and methods for manipulating the responses. The invention further provides a common gamma chain independent receptor on mast cells capable of mediating the mentioned effects of **Ig-LC**. In response to activation of the pathway of which the found receptor is a part, a mast cell is activated and stimulated to degranulate.

L25 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
2003:717226 Document No. 139:229273 Ig light chains mediate hypersensitivity responses. Nijkamp, Franciscus Petrus; Kraneveld, Aletta Desiree; Redegeld, Franciscus Antonius Maria (Fornix Biosciences N. V., Neth.). Eur. Pat. Appl. EP 1342779 A1 20030910, 33 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-75874 20020306.

AB Ig light chains (**Ig-LC**) are produced in excess in animals compared to heavy chains. The present invention implicates these **Ig-LC** in hypersensitivity responses and provides means and methods for manipulating the responses. The invention further provides a receptor on mast cells capable of mediating the mentioned effects of **Ig-LC**.

L25 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 1
2002271181 Document Number: 22006128. PubMed ID: 12012110. Light chain myeloma plasma cells induce a strong cell-mediated immune response mainly directed against the monoclonal light chain determinants in a murine experimental model. Galea Horia Radu; Denizot Yves; Cogne Michel. (Immunology Laboratory, CNRS UMR 6101, University Hospital, 2 rue du Dr. Marcland, 87042 Limoges, France.) CANCER IMMUNOLOGY, IMMUNOTHERAPY, (2002

Jun) 51 (4) 229-34. Journal code: 8605732. ISSN: 0340-7004. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB An important goal for the treatment of human B cell malignancies lies in the induction of an active immune response directed against the tumoral clone, and more particularly against antigenic determinants of the monoclonal immunoglobulin (Ig). The presence of idiotype-reactive T-cells in patients with multiple myeloma has been previously reported, and strategies to increase their responsiveness towards the malignant plasma cells are being actively explored. Light chain (LC) myeloma is often an aggressive form of the disease, regarding which antitumoral immunity has not yet been studied. Here, we investigated in an experimental murine model a secreted monoclonal LC that may behave as a strong tumor antigen after immunization of animals with mitomycin C-treated malignant plasma cells producing monoclonal Ig. Non-dividing plasma cells were utilized as a cell suspension to immunize the mice intraperitoneally (i.p.). The immunized mice produced anti-Ig LC antibodies, mounted a cell-mediated response mainly directed against the monoclonal LC determinants, and survived tumor challenge with significant frequency. These results suggest that plasma cells are capable of presenting antigenic determinants derived from a secreted monoclonal LC in an MHC class I context, and of predominantly inducing a monoclonal Ig-specific T-cell response which can contribute to tumor rejection.

L25 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

2001:135552 Document No. 134:308348 Hsp70 and antifibrillogenic peptides promote degradation and inhibit intracellular aggregation of amyloidogenic light chains. Dul, Jeanne L.; Davis, David P.; Williamson, Edward K.; Stevens, Fred J.; Argon, Yair (Department of Pathology and Committee on Immunology, The University of Chicago, Chicago, IL, 60637, USA). Journal of Cell Biology, 152(4), 705-715 (English) 2001. CODEN: JCLBA3. ISSN: 0021-9525. Publisher: Rockefeller University Press.

AB In light chain (LC) amyloidosis an Ig LC assembles into fibrils that are deposited in various tissues. Little is known about how these fibrils form in vivo. We previously showed that a known amyloidogenic LC, SMA, can give rise to amyloid fibrils in vitro when a segment of one of its .beta. sheets undergoes a conformational change, exposing an Hsp70 binding site. To examine SMA aggregation in vivo, we expressed it and its wild-type counterpart, LEN, in COS cells. While LEN is rapidly oxidized and subsequently secreted, newly synthesized SMA remains in the reduced state. Most SMA mols. are dislocated out of the ER into the cytosol, where they are ubiquitinated and degraded by proteasomes. A parallel pathway for mols. that are not degraded is condensation into perinuclear aggresomes that are surrounded by vimentin-contg. intermediate filaments and are dependent upon intact microtubules. Inhibition of proteasome activity shifts the balance toward aggresome formation. Intracellular aggregation is decreased and targeting to proteasomes improved by overexpression of the cytosolic chaperone Hsp70. Importantly, transduction into the cell of an Hsp70 target peptide, derived from the LC sequence, also reduces aggresome formation and increases SMA degrdn. These results demonstrate that an amyloidogenic LC can aggregate intracellularly despite the common presentation of extracellular aggregates, and that a similar mol. surface mediates both in vitro fibril formation and in vivo aggregation. Furthermore, rationally designed peptides can be used to suppress this aggregation and may provide a feasible therapeutic approach.

L25 ANSWER 5 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2

2001:197724 Document No.: PREV200100197724. Thermodynamic stability and conformation of a moderately aggressive amyloidogenic kappa I immunoglobulin light chain (IG LC) CLU. Walsh, Mary T. [Reprint author]; Wally, Jeremy [Reprint author]. Boston University School of Medicine, 715 Albany Street, Boston, MA, 02118-2526, USA. Biophysical Journal, (January, 2001) Vol. 80, No. 1 Part 2, pp. 559a-560a. print. Meeting Info.: 45th Annual Meeting of the Biophysical Society. Boston,

Massachusetts, USA. February 17-21, 2001. Biophysical Society.
CODEN: BIOJAU. ISSN: 0006-3495. Language: English.

L25 ANSWER 6 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:384314 Document No.: PREV200100384314. Unassembled Ig heavy chains do not
cycle from BiP in vivo but require light chains to trigger their release.
Vanhove, Marc; Usherwood, Young-Kwang; Hendershot, Linda M. [Reprint
author]. Department of Tumor Cell Biology, St. Jude Children's Research
Hospital, 332 North Lauderdale, Memphis, TN, 38105, USA.
linda.hendershot@stjude.org. Immunity, (July, 2001) Vol. 15, No. 1, pp.
105-114. print.

ISSN: 1074-7613. Language: English.

AB Unassembled Ig heavy chains are retained in the ER via the binding of BiP
to the CH1 domain, which remains unoxidized. Interestingly, this domain
folds rapidly, albeit nonproductively, when heavy chains are released from
BiP in vitro with ATP. The in vivo cycling of BiP from heavy chains was
monitored using BiP ATPase mutants as kinetic traps. Our data suggest
that BiP does not cycle from the CH1 domain of free heavy chains.
However, heavy and light chain assembly occurs rapidly and requires the
ATP-dependent release of BiP. We propose that BiP's ATPase cycle is
stalled or nonproductive when it is bound to free heavy chains. The
binding of light chains to the complex reactivates the cycle and releases
BiP.

L25 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
2000:53707 Document No. 132:106970 Compound capable of inhibiting the
binding of a protein to mast cells, use of the compound for the
preparation of a drug, a pharmaceutical composition, a method of
diagnosing a disease, and a method of selection. Redegeld, Franciscus
Antonius Maria; Kraneveld, Aletta Desiree; Nijkamp, Franciscus Petrus
(Universiteit Utrecht, Neth.). PCT Int. Appl. WO 2000002915 A1 20000120,
27 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG,
MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,
GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English).
CODEN: PIXXD2. APPLICATION: WO 1999-NL430 19990707. PRIORITY: NL
1998-1009601 19980709.

AB The invention relates to a compd. inhibiting the binding of the free light
chain of Ig (Ig LC) to mast cells. It has been found
that Ig LC is the agent responsible for the
sensitization of mast cells. The compds. according to the invention can
thus be used for the prepn. of a drug for the treatment of a disease whose
symptom is an elevated Ig LC concn. in serum or spinal
fluid. The invention also relates to a method of screening a series of
compds. on their ability to reduce the sensitization of mast cells.

L25 ANSWER 8 OF 13 MEDLINE on STN DUPLICATE 3
1999244927 Document Number: 99244927. PubMed ID: 10228037. Organ-specific
(localized) synthesis of Ig light chain amyloid. Hamidi Asl K; Liepnieks J
J; Nakamura M; Benson M D. (Department of Medical and Molecular Genetics,
Indiana University School of Medicine, Richard L. Roudebush Veteran
Affairs Medical Center, Indianapolis 46202, USA.) JOURNAL OF IMMUNOLOGY,
(1999 May 1) 162 (9) 5556-60. Journal code: 2985117R. ISSN: 0022-1767.
Pub. country: United States. Language: English.

AB Ig amyloidosis is usually a systemic disease with multisystem involvement.
However, in a significant number of cases amyloid deposition is limited to
one specific organ. It has not been determined if the Ig light chain (LC)
amyloid precursor protein in localized amyloidosis is synthesized by
circulating plasma cells with targeting of the amyloid fibril-forming
process to one specific organ, or whether the synthesis of Ig
LC and fibril formation occurs entirely as a localized process.
In the present study local synthesis of an amyloid fibril precursor LC was

investigated. Amyloid fibrils were isolated from a ureter that was obstructed by extensive infiltration of the wall with amyloid. Amino acid sequence analysis of the isolated fibril subunit protein proved it to be derived from a lambdaII Ig LC. Plasma cells within the lesion stained positively with labeled anti-lambda Ab and by in situ hybridization using an oligonucleotide probe specific for lambda-LC mRNA. RT-PCR of mRNA extracted from the tumor and direct DNA sequencing gave the nucleotide sequence coding specifically for the lambdaII amyloid subunit protein, thus confirming local synthesis of the LC protein.

- L25 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 4
1999162588 Document Number: 99162588. PubMed ID: 10051625. Induction of Ig light chain gene rearrangement in heavy chain-deficient B cells by activated Ras. Shaw A C; Swat W; Davidson L; Alt F W. (Howard Hughes Medical Institute, Boston, MA 02115, USA.. alt@rascal.med.harvard.edu) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 2) 96 (5) 2239-43. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
- AB During B cell development, rearrangement and expression of Ig heavy chain (HC) genes promote development and expansion of pre-B cells accompanied by the onset of Ig light chain (LC) variable region gene assembly. To elucidate the signaling pathways that control these events, we have tested the ability of activated Ras expression to promote B cell differentiation to the stage of LC gene rearrangement in the absence of Ig HC gene expression. For this purpose, we introduced an activated Ras expression construct into JH-deleted embryonic stem cells that lack the ability to assemble HC variable region genes and assayed differentiation potential by recombination activating gene (RAG) 2-deficient blastocyst complementation. We found that activated Ras expression induces the progression of B lineage cells beyond the developmental checkpoint ordinarily controlled by mu HC. Such Ras/JH-deleted B cells accumulate in the periphery but continue to express markers associated with precursor B cells including RAG gene products. These peripheral Ras/JH-deleted B cell populations show extensive Ig LC gene rearrangement but maintain an extent of kappa LC gene rearrangement and a preference for kappa over lambda LC gene rearrangement similar to that of wild-type B cells. We discuss these findings in the context of potential mechanisms that may regulate Ig LC gene rearrangement.

- L25 ANSWER 10 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:960545 The Genuine Article (R) Number: 263NE. Embryotoxicity screening using embryonic stem cells in vitro: Correlation to in vivo teratogenicity . Scholz G (Reprint); Pohl I; Genschow E; Klemm M; Spielmann H. BGVV, ZEBET, DIEDERSDORFER WEG 1, D-12277 BERLIN, GERMANY (Reprint). CELLS TISSUES ORGANS (DEC 1999) Vol. 165, No. 3-4, pp. 203-211. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1422-6405 . Pub. country: GERMANY. Language: English.
- *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

- AB Blastocyst-derived pluripotent embryonic stem (ES) cells of the mouse can be induced to differentiate in culture into a variety of cell types, including cardiac muscle cells. The embryonic stem cell test that makes use of the differentiation of ES cells into cardiomyocytes in a standardized in vitro model was developed to offer an alternative method to comprehensive in vivo studies in reproductive toxicology about toxic effects of chemicals. ES cells of the mouse cell line D3 are investigated for their preserved capability to differentiate following drug exposure, and both ES cells and differentiated fibroblast cells of the mouse cell line 3T3 are comparatively analyzed for effects on viability. The following endpoints are used to classify the embryotoxic potential of chemicals into three classes of in vitro embryotoxicity (non-, weakly or strongly embryotoxic). These endpoints are: (1) the inhibition of differentiation of ES cells into cardiomyocytes after 10 days of treatment, and the decrease of viability (cytotoxicity) of (2) 3T3 cells and (3) ES cells after 10 days of treatment, determined by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test.

50% inhibition concentrations for differentiation (ID50) and cytotoxicity (IC(50)D3 and IC(50)3T3) are calculated from concentration-response curves. Applying linear analysis of discriminance, a biostatistical prediction model (PM) was developed. This procedure identified three variables, the Ig(1C(50)D3), the Ig(IC(50)3T3) and the relative distance between IC(50)3T3 and ID50, that improved the separation of the three classes of embryotoxicity compared to the prediction model that was originally proposed after test development. Unlike the original PM, the improved PM incorporates as one variable the relative distance between IC(50)3T3 and ID50, instead of the ratio ID50/IC(50)D3 that was used previously. Copyright (C) 1999 S. Karger AG, Basel.

L25 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1999:6462 Document No. 130:208527 Regulation of immunoglobulin light chain isotype expression. Gorman, James R.; Alt, Frederick W. (Howard Hughes Medical Institute, The Children's Hospital, Boston, MA, 02115, USA). *Advances in Immunology*, 69, 113-181 (English) 1998. CODEN: ADIMAV. ISSN: 0065-2776. Publisher: Academic Press.

AB A review with approx. 350 refs. Discussed are: antibody mols. and Ig gene assembly (historical background; assembly of genes from multiple V, (D), and J segments; organization of Ig loci; transcriptional regulation of IgL loci); allelic exclusion of Ig loci (regulated and stochastic models of allelic exclusion; ordered HC rearrangement and HC allelic exclusion; role of .mu. protein and the pre-BCR in HC allelic exclusion and prelymphocyte developmental progression; RAG gene expression and HC allelic exclusion; role of HC and pre-BCR in LC locus activation; LC allelic exclusion; possible mechanisms of asynchronous HC or LC gene rearrangement); tissue- and stage-specific control of Ig light .kappa. expression (germline transcription of murine IgL .kappa. loci; germline transcription of human IgL .kappa. loci; possible functions of IgL .kappa. germline transcripts; role of .kappa. enhancers in expression of rearranged .kappa. genes; stage specificity of 3'E.kappa. activity); and regulation of Ig light chain gene rearrangement (models for preferential LC rearrangement and isotype exclusion; role of RS/.kappa.de rearrangement in Ig LC gene rearrangement; control and function of .kappa.:.lambda. ratios in mice and humans). (c) 1998 Academic Press.

L25 ANSWER 12 OF 13 MEDLINE on STN

DUPLICATE 5

1998113387 Document Number: 98113387. PubMed ID: 9451427.

Clinico-prognostic relevance of quantitative immunophenotyping in B-cell chronic lymphocytic leukemia with emphasis on the expression of CD20 antigen and surface immunoglobulins. Molica S; Levato D; Dattilo A; Mannella A. (Divisione Ematologia, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro, Italy.) *EUROPEAN JOURNAL OF HAEMATOLOGY*, (1998 Jan) 60 (1) 47-52. Journal code: 8703985. ISSN: 0902-4441. Pub. country: Denmark. Language: English.

AB Expression of CD20, evaluated as antibody binding capacity (ABC) (i.e. absolute number of molecules of antibody per cell), was analyzed using flow cytometry on leukemic cells of 93 previously untreated patients, all fulfilling strict criteria of "immunologically typical" (i.e. CD5+, CD23+) B-cell chronic lymphocytic leukemia (CLL). Although changes of CD20 antigen density did not correlate with clinical parameters representative of either tumor mass (i.e. clinical stage, histological pattern of bone marrow involvement, absolute peripheral blood lymphocytosis) or disease progression (i.e. lymphocyte doubling time), a trend toward a better life-expectancy was observed in the low CD20 expression group compared with the high CD20 expression group (p = 0.05; relative risk of death, 0.51, 95% confidence interval, 0.24-1.04). Given the correlation between CD20 ABC and mean fluorescence intensity (MFI) of light chain (LC) surface immunoglobulins (Sm Ig) (r = 0.481, p < 0.0001), as well as the impact of MFI of Sm Ig LC on overall survival (p = 0.01; relative risk of death 0.44; 95% confidence interval, 0.10 to 0.76), we tried to verify whether a combination of B-cell markers, evaluated in a quantitative manner, could have additive prognostic properties. To this purpose we gave a value of 1 or 0 to each B-cell

marker according to whether it was expressed at a low (i.e. CD20 ABC < 17.9 x 10(3) molecules/cell, MFI of LC Sm Ig < 100) or high (i.e. CD20 ABC > or = 17.9 x 10(3) molecules/cell, MFI of LC Sm Ig > or = 100) level thus allowing patient stratification into two groups with scores of 2 and 0-1, respectively. Survival of patients who scored 2 was significantly longer respectively. Survival of patients who scored 2 was significantly longer than that of patients who scored 0-1 (p = 0.02; relative risk of death, 0.44; 95% confidence interval, 0.22-0.72). However, when quantitative changes of CD20 antigen and LC Sm Ig expression, either alone or in combination, were simultaneously analyzed in a Cox model which included usual clinico-hematological features, only absolute peripheral blood lymphocytosis (p = 0.0001) and Binet clinical stages (p = 0.0001) maintained their prognostic power unmodified. Although variability of CD20 and Sm Ig expression make it possible to appreciate biological heterogeneity of B-cell CLL better, however, they cannot substitute well-established clinico-hematological features in the prognostic assessment of B-CLL patients.

L25 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1984:49692 Document No. 100:49692 An immunoenzymic technique to determine without prior purification the isoelectric point of monoclonal components in the serum or urine of patients with monoclonal gammopathy. Melcion, Celine; Baudouin, Beatrice; Verroust, Pierre (Hop. Tenon, Paris, 75020, Fr.). Developments in Immunology (Elsevier), 18(Immunoenzym. Tech.), 337-40 (English) 1983. CODEN: DEIMD6. ISSN: 0163-5921.

AB A method was developed for the detection of monoclonal Ig .lambda. and .kappa. light chains (LC) present in serum and urine samples of patients with myeloma. Serum and urine samples were submitted to isoelectrofocusing in thin slabs of 5% polyacrylamide gel. The proteins were then transferred to cellulose nitrate sheets and incubated with rabbit anti-.lambda. or anti-.kappa. antisera. After 3 washings, purified .lambda. or .kappa. LC coupled to peroxidase were added to the proteins. The bound enzyme was detected by incubation with 4-chloronaphthol. Using this method, no evidence was found that LC with the highest isoelec. point (pI) were assocd. with more severe human renal failure. Instead, the most severe cases of renal insufficiency were obsd. in patients who produced LC with the lowest pI. This assay is an easy, quick, and specific way to analyze monoclonal Ig LC. Assay sensitivity varied with individual proteins from 100-500 ng LC/sample.

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	ENTRY	SESSION
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